AD-785 017

CARDIOPULMONARY EFFECTS OF VOLUME LOADING OF PRIMATES IN ENDOTOXIN SHOCK

L. J. Greenfield, et al

Oklahoma University Health Sciences Center

AD 785 017

Prepared for:

Office of Naval Research

17 June 1974

DISTRIBUTED BY:

NTIS

National Technical Information Service
U. S. DEPARTMENT OF COMMERCE
5285 Port Royal Road, Springfield Va. 22151

UNCLASSIFIED
Security Classification

AD785017

DOCUMENT CONTROL DATA - R & D

Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)

UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER
OKLAHOMA CITY, OKLAHOMA

2a. REPORT SECURITY CLASSIFICATION
UNCLASSIFIED

2b. GROUP
UNCLASSIFIED

3. REPORT TITLE

CARDIOPULMONARY EFFECTS OF VOLUME LOADING OF PRIMATES IN ENDOTOXIN SHOCK

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

Technical Report

5. AUTHOR(S) (First name, middle initial, last name)

L. J. Greenfield, R. H. Jackson, R. C. Elkins, J. J. Coalson, L. B. Hinshaw

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
17 June 1974	29	29

8a. CONTRACT OR GRANT NO	9a. ORIGINATOR'S REPORT NUMBER(S)
N00014-68-A-0496 b. PROJECT NO NR 105-516 c d	87 9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)

10. DISTRIBUTION STATEMENT

Distribution of this report is unlimited

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
	Office of Naval Research

13. ABSTRACT

Myocardial performance was evaluated in rhesus monkeys after endotoxin shock, and the responses to fluid loading with colloid measured in both anesthetized control and experimental groups. Minute work and cardiac output (CO) were decreased in 5 monkeys after 6 hours endotoxin to levels significantly below control values. Infusing colloid to a mean LVEDP of 12-15 mm Hg increased both CO and minute work significantly but they remained one-half that of the control group of 4 primates after fluid loading. Improved cardiac performance persisted after infusion through a 30-minute recovery stage when LVEDP returned to normal. Simultaneous PAW pressures showed some correlation with LVEDP reading up to 6 mm Hg, but above that level the PAW underestimated the LVEDP by 3-6 mm Hg. Microscopic study showed that fluid loading produced comparable pulmonary edema in both groups, but endotoxin produced ultrastructural capillary lesions. A normal PAW pressure after fluid administration can occur after transient overloading of the left ventricle. Since interstitial pulmonary edema is not readily reversible, persistent respiratory insufficiency may result and the cause be unsuspected unless ventricular filling pressures are monitored during fluid administration.

Reproduced by
NATIONAL TECHNICAL
INFORMATION SERVICE
U S Department of Commerce
Springfield VA 22151

1<

DD FORM 1 NOV 68 1473 (PAGE 1)
S/N 0101-807-6811

UNCLASSIFIED
Security Classification

A-31408

OFFICE OF NAVAL RESEARCH

Contract N00014-68-A-0496

Project NR 105-516

TECHNICAL REPORT NO. 87

CARDIOPULMONARY EFFECTS OF VOLUME LOADING OF PRIMATES IN ENDOTOXIN SHOCK

L. J. Greenfield, R. H. Jackson, R. C. Elkins,

J. J. Coalson, and L. B. Hinshaw

Prepared for Publication

in Surgery

University of Oklahoma Health Sciences Center
Departments of Surgery and Physiology
Oklahoma City, Oklahoma

17 June 1974

Reproduction in whole or in part is permitted for any purpose of the United States Government

Distribution of this report is unlimited

2<

Variable observations have been reported on the relationship between pulmonary arterial wedge (PAW) pressures and left atrial (LA) pressures measured consecutively in patients with valvular or congenital heart disease, or simultaneously in experimental animals (3,6,28). Since LA pressure is the same as left ventricular pressure during diastole in the absence of mitral valve disease, it is usually assumed that left ventricular end-diastolic pressure (LVEDP) has the same relationship to PAW pressure as to the LA pressure during ventricular diastole. Consequently, the ready accessibility of pulmonary arterial pressure measurement with the development of flow-directed balloon catheters can provide an indirect bedside approach to assessment of left ventricular function. However, variability of these measurements particularly in shock, have concerned the clinician attempting to improve cardiac output by volume loading without producing pulmonary edema.

Cardiac output (CO) usually shows a steady decline in human septic shock (21) but there is disagreement regarding the pathogenesis of cardiac failure in man (7) or the nonhuman primate (8). The development of early myocardial failure in clinical sepsis (20) could account for the lowered CO but a significant decrease in venous return to the heart is the more likely explanation and has been confirmed in the dog (27) and rhesus monkey (2). Recent studies using the primate model for vascular studies (12,15,16,22,23) indicate that its hemodynamic characteristics make it particularly suitable as a shock model.

The present study was designed to evaluate primate myocardial performance in endotoxin shock and the cardiopulmonary response to fluid loading with colloid. Also tested was the validity of using PAW pressure to assess left ventricular response as opposed to direct catheterization of the left ventricle to measure LVEDP.

METHODS

Eleven healthy adult rhesus monkeys (Macaca mulatta) of both sexes were selected for study. They were anesthetized by intravenous administration of 20-25 mg of pentobarbital per kg of body weight. A #5 Lehman catheter was threaded into the left ventricle and a #5 balloon-tipped catheter was positioned in the left pulmonary artery from the femoral artery and vein. A #19 Teflon needle was introduced into the opposite femoral artery and a #6 Goodale-Lubin catheter was advanced into the right atrium. All catheters were positioned under direct fluoroscopic control. A cuffed endotracheal tube was inserted and the cuff inflated to permit the collection of expired gases and allow for periodic positive pressure ventilation to prevent atelectasis. The endotracheal tube was connected to a Sierra valve with an 8 ml dead space, and expired gases were collected in a water-sealed spirometer. Expired gases and arterial and mixed venous blood were analyzed for pH, pCO_2 and pO_2 on an analyzer (Instrumentation Laboratories Model 113) calibrated with known gas mixtures prior to each determination. Oxygen content of arterial and mixed venous blood was measured directly (Lexington, Instruments, Lex-O_2-Con). Oxygen consumption ($\dot{V}_{O_2}$) was calculated using these data and cardiac output (CO) was calculated by the Fick method. Left ventricular end-diastolic pressure (LVEDP) and pulmonary arterial wedge pressure (PAW) were recorded using a single Statham P23Db transducer. Systemic arterial pressure (SAP) was recorded using a separate transducer on a multichannel oscillographic recorder. Minute work was calculated from the formula:

$$\frac{(MSAP - LVEDP)\ CO\ (1.36)}{100}$$

which is a modification of Ross' formula for stroke work (24) where MSAP and LVEDP are in mm Hg, CO is in L/min and minute work is expressed in kg-meters. All pressure measurements were recorded simultaneously.

After obtaining baseline hemodynamic, respiratory and blood gas data, 5 monkeys were injected with 6 mg of purified E. coli endotoxin (Difco; Detroit) per kg of body weight and 4 monkeys were given a saline blank of equal volume over a 15-min period. Six hours after the injections of endotoxin or saline, a second set of baseline measurements was obtained and the colloid infusion started (Plasmanate, Cutter Laboratories). The colloid was administered in increments of 5 ml/kg of body weight until an LVEDP of 12-15 mm Hg was reached, with measurements taken after each increment. The time of infusion of each increment was approximately 10 minutes. After an LVEDP of 12-15 mm Hg was reached, the animal was allowed to recover for a period of 30 minutes and measurements repeated.

Five to 10 minutes before sacrificing the animal with an overdose of pentobarbital, the animals were injected with 1 ml/kg of Pelikan ink. A thoracotomy was performed and samples were taken from one lung and the left ventricle by light and electron microscopy. For light microscopic studies specimens were placed in Carnoy's fixative and sections were stained by hematoxylin and eosin, phosphotungstic acid, hematoxylin, and Van Gieson elastica. Specimens obtained for ultrastructural study were placed in Zetterqvist's fixative, dehydrated in ascending grades of ethanol, and embedded in Lpon 812 and Araldite. Thin sections were stained with Reynold's lead citrate and uranyl acetate and examined with an RCA EMU 3-5 and Hitachi HS-7 electron microscopes.

Whole inflated lung samples were blotted dry and wet-to-dry weight ratios obtained after oven drying for a minimum of 48 hours. Two gram samples of lung tissue also were minced in saline for determination of pulmonary surfactant on the surfactometer as described previously (9).

RESULTS

Classical signs of endotoxin shock were observed in the injected group of monkeys 6 hours after endotoxin administration (2,4,13,29). Mean heart rate (HR) had increased from control values of 180/min to 234/min after 6 hours ($p<0.05$). Mean hematocrit had increased from 41.4% to 45.8% ($p<0.05$) after 6 hours and mean HCO_3^- fell from 25.8 to 17.0 meq/l ($p<0.05$). In addition, the mean cardiac output (CO) had dropped from 0.120 liters/min/kg to 0.082 liters/min/kg ($p<0.05$) and mean systemic arterial pressure (MSAP) had dropped from 157 mm Hg to 112 mm Hg, although the latter change was not significant. Minimal changes occurred in these parameters in the control monkeys, and none was significant statistically.

The effects produced by infusion of colloid were compared immediately after infusion and after the recovery period in controls and in the endotoxin group. The mean HR in the endotoxin monkeys decreased from 234/min at 6 hours to 205/min after fluid loading ($p<0.05$) and fell further to 199/min after the 30-minute recovery period ($p<0.05$). This rate was still significantly faster than the initial control rate. No decrease in mean heart rate occurred after fluid loading in the control monkeys, and after recovery the rate had not changed (Talbe 1).

Mean hematocrit in the endotoxin group of monkeys dropped from 45.8% at 6 hours to 30.0% after fluid loading ($p<0.05$) and remained at 31% after the recovery period ($p<0.05$). This was still significantly below the control value of 41.4%. The mean hematocrit for the control monkeys fell from 42% to 34.5% ($p<0.05$) after fluid loading and continued to fall to 33.5% after the 30-minute recovery period. This also was significantly below the control value (Fig. 1).

The mean HCO_3^- for the endotoxin group fell significantly after 6 hours from the control value of 25.8 meq/l and then increased slightly from 17 meq/l

to 19.2 meq/l after fluid loading but the change was not significant and no significant change occurred after the 30 minute recovery period. The mean HCO_3 for the control monkeys showed no significant change from the initial or 6-hour period values. The mean arterial pH was elevated slightly in control animals after 6 hours but did not change significantly in the endotoxin group. Values in the endotoxin group, however, were significantly lower than controls after loading and the recovery period (Fig. 2). Control animals increased their alveolar-arterial (A-a) O_2 gradient from control values of 17.7± 7.0 mm Hg to 39.9 ± 7.6 mm Hg after 6 hours anesthesia and further to 55.8 ± 2.2 mm Hg after loading with depression of the PaO_2 to 49 mm Hg. Presumably this hypoxia was secondary to atelectasis resulting in hyperventilation and decreased $PaCO_2$. No significant change in A-a gradient was noted in the endotoxin group. Arterial pO_2 was slightly higher in the endotoxin group after 6 hours and associated with a greatly increased respiratory rate and reduced $PaCO_2$ (Fig. 3) although the differences were not statistically significant.

The endotoxin group showed further depression of average MSAP from 112 mm Hg at 6 hours to 94 mm Hg after loading with 30 cc colloid/kg body weight and then rose insignificantly to 96 mm Hg after the 30 minute recovery period (Table 2 and Fig. 4). This pressure remained significantly lower than the average control value of 157 mm Hg. Control monkeys experienced a significant rise in average MSAP from 130 mm Hg to 147.5 mm Hg after loading with 20 cc colloid/kg body weight, but after recovery MSAP averaged 138 mm Hg, which was not significantly different from the control pressure (136 mm Hg). The PAW was found to be a relatively inaccurate method for determining LVEDP tending to overestimate slightly up to 5 mm Hg and progressively to underestimate the true LVEDP at higher values so that above an LVEDP of 10 mm Hg the error was 4-6 mm Hg (Fig. 5).

Mean CO/kg for the endotoxin group showed a significant fall at 6 hours

compared to control animals but increased from .082 liters/min/kg at 6 hours to .158 liters/min/kg after fluid loading, and showed a slight further rise to .189 liters/min/kg after the 30-minute recovery period (Fig. 6). This level of CO was greater than the initial output of the endotoxin group (.120 liters/min/kg) and not significantly different from the control group. Fluid loading increased the CO of the control monkeys from .148 liters/min/kg to .233 liters/min/kg which returned after recovery to .82 liters/min/kg.

Fluid loading with 20 cc colloid/kg body weight raised the LVEDP to 12-15 mm Hg in all but one of the control monkeys while the same volume of infusion in the endotoxin monkeys failed uniformly to increase the LVEDP above 10 mm Hg (Table 3). Three of the 5 endotoxin treated monkeys finally reached an LVEDP of 15 mm Hg after infusion of a total of 30 cc colloid/kg body weight, while one required 35 cc/kg and the other one 40 cc/kg before reaching an LVEDP of 15 mm Hg. After fluid loading the endotoxin group to an LVEDP of 15 mm Hg, recovery for 30 minutes resulted in a mean LVEDP of 4.2 mm Hg, which was not significantly different from the control value of 2.6 mm Hg. Similarly, the control monkeys recovered to a mean LVEDP of 3 mm Hg after infusion which did not differ from the control value of 2.1 mm Hg. The correlation between PAW and LVED pressures was significant with a coefficient of $R=0.89$ ($p<.005$). No significant difference was noted between the groups but the correlation was significantly different from unity (Fig. 5).

Calculated minute work/kg of the heart fell significantly from 0.247 kg/meters/kg at control to 0.117 kg/meters/kg after 6 hours in the endotoxin group, while it rose insignificantly from 0.221 to 0.262 kg/meters/kg in the control monkeys. Fluid loading raised the minute work of the endotoxin monkeys to 0.190 kg/meters/kg and it rose further to 0.198 kg/meters/kg after the recovery period. Fluid loading raised the minute work of the control monkeys

from 0.262 to 0.406 kg/meters/kg after which it decreased to 0.336 kg/meters/kg (Fig. 6). Calculated pulmonary arterial input resistance increased in both groups in response to fluid loading by an average of 67% in the endotoxin animals and 84% in the controls. The measured wet-to-dry weight ratios of excised lung were abnormally elevated in both groups to 6.17 ± 2.3 in controls and 6.35 ± .70 in the endotoxin group, but the difference between the groups was not statistically significant. The minimum surface tensions of lung extracts were also abnormally high in both groups averaging 23.6 dynes/cm in the controls and 22.8 dynes/cm in the endotoxin group. Hysteresis loop areas were similarly depressed to 1.10 in^2 in the endotoxin group.

Light microscopically, the Pelikan ink was noted to fill extensively the vascular beds in both the normal and experimental animals. In heart sections both the control and the endotoxin treated groups showed comparable degrees of perinuclear edema. In lung sections, endotoxin treated animals showed more alveolar space rounding, alveolar wall collapse, and pulmonary edema (Fig. 7). Ultrastructural changes in the lung in the endotoxin-treated specimens showed more extensive endothelial swelling when compared to loaded controls (Fig. 8), occasional endothelial cell lifting from the underlying basement membrane and an abundance of white blood cells and platelets within the lumina of the capillaries (Fig. 9). Varying degrees of perivascular space edema were seen in both the control and experimental groups and this feature was not helpful in distinguishing the two groups. The ink tracer was noted infrequently in the alveolar space transudate but the method of transfer across the endothelial barrier could not be defined. The intercellular junctions between the endothelial cells only occasionally showed increased granularity; and no Pelikan ink could be seen within the pinocytotic vesicles of the endothelial cytoplasm.

In ultrastructural sections of the heart, the control groups showed mild perinuclear edema, lack of mitochondrial swelling, normal interfiber spaces, and normal capillary endothelium (Fig. 10). The presence of ink was noted in the capillary lumina and only rarely outside the vascular lumina. At no time could the ink be found in the pinocytotic vesicles or within the intercellular spaces.

When compared to the control group, the endotoxin-treated hearts showed more extensive edematous changes. Most prominently seen was an endothelial lesion consisting of marked edema with resultant swelling of the capillary endothelium projecting into the vascular lumen (Fig. 11). The edema was seen as individual cell swelling but quite frequently the entire endothelial lining would show marked edematous change. Occasional bleb-like structures were seen in the edematous endothelial myocardial cells (Fig. 12). Free blebs were seen frequently in the capillary lumina. Multiple low power micrographs revealed more extensive fluid accumulations within the interfiber spaces with marked separation of the perivascular bundles of collagen. In addition, there was marked intrafiber edema with separation of the myofibrils. Many animals showed focal mitochondrial swelling but no marked disruption of mitochondrial membranes was noted and the mitochondrial changes would be considered reversible in nature.

DISCUSSION

Both groups of monkeys demonstrated significant interstitial pulmonary edema following fluid loading to a transient LVEDP of 12-15 mm Hg which did not resolve after the recovery period with return of LVEDP to normal levels. In the group administered endotoxin plus fluid loading the pulmonary edema was more pronounced presumably due to the endothelial damage seen ultrastructurally. The perivascular space edema in both groups as well as the white blood cells and

platelets found in the lumina of the capillaries of the endotoxin group as found in monkeys and dogs by other investigators (5,14,17,22) may account for increased resistance to flow in the pulmonary capillaries in both groups, and explain the pressure gradient between the values of the PAW and LVEDP observed at higher LVEDP during the fluid loading. The observed increase in pulmonary arterial input resistance seen in both groups supports this hypothesis and explains the uniformity of the relationship between PAW and LVEDP seen in both groups.

In a recent publication, Kusajima et al. (18) reported an early small pulmonary vein constriction (active occlusion of vessels) and later capillary obstruction (passive occlusion of vessels) in dogs after hemorrhagic shock, which resulted in a 5 mm Hg pressure gradient between the PAW and small pulmonary vein. Hinshaw et al. (17) observed massive sequestration of polymorphonuclear leukocytes in pulmonary capillaries which produced an obstruction to blood flow (passive occlusion of vessels), and pulmonary venous constriction (active occlusion of vessels) in adult anesthetized rhesus monkeys with intravenously administered lethal doses of E. coli endotoxin. Both of these studies suggest that the effects of shock on the pulmonary vascular bed have both a passive and active occlusive action which can dampen the transmission of LVEDP to the PAW catheter tip and may explain the observed pressure gradient. Clinical studies in patients with mitral stenosis or bronchogenic carcinoma (6) showed a direct correlation between PAW and LVEDP and similar reliability has been demonstrated between PA end-diastolic pressure (PAEDP) and LVEDP in patients in shock (25). When there is left ventricular dysfunction, however, the LVEDP is observed to be consistently higher than PAEDP and the disparity is further exaggerated by increasing systemic pressure with methoxamine (1). The data obtained from this study showed a linear relationship of the PAW to the LVEDP, but it differed from

unity and showed that the PAW pressure tends to be 3-6 mm Hg lower than the LVEDP at higher ventricular filling pressures in this preparation. These observations suggest that the validity of PAW and PAEDP in resuscitation may be questioned and may not insure the avoidance of fluid overloading and transient left ventricular dysfunction.

The interstitial pulmonary edema induced in both control and endotoxin groups resulted in comparable increases in wet-to-dry weight ratios and reductions in pulmonary surfactant. Since colloid was used rather than a crystalloid it is not necessary to consider the added deleterious effects of hemodilution and alteration of the Starling capillary relationship although the measured osmolality of the colloid used was less than isooncotic (202 mosm/1). The fact that the LVEDP returned to normal levels 30 minutes after fluid infusion has interesting implications. Obviously, a single measurement of a normal LVEDP cannot reflect a previously elevated LVEDP, during which time pulmonary venous hypertension and edema could have occurred. Thus, the transient ventricular overloading can initiate pulmonary edema which is not readily reversible as has been demonstrated in isolated lungs made edematous by hydrostatic pressure (11). The interstitial pulmonary edema produced in this manner remains even when pulmonary venous pressure is restored to normal or negative values. It seems reasonable then to suggest that many cases of the "wet-lung syndrome" associated with shock and resuscitation may in fact have been initiated by fluids administered rapidly for resuscitation producing transient ventricular overload not excluded by a subsequently measured normal PAW pressure (Fig. 13).

The significantly lower CO for the endotoxin monkeys after 6 hours as compared to control monkeys could reflect either decreased venous return, as demonstrated by other investigators (2,15,27), or myocardial depression or both. Even though the endotoxin monkeys received an average of almost twice as

much colloid as the control monkeys, their CO increased to only half the CO of the control monkeys. This suggests that myocardial performance was impaired directly as a result of the 6-hour endotoxin insult in addition to the decreased venous return corrected by volume repletion (Fig. 6).

The significant drop in calculated minute work of the heart after 6 hours' exposure to endotoxin and the average minute work response to volume loading performed by the endotoxin-treated hearts was less than half the minute work performed by the control hearts after fluid loading with colloid (Figs. 6 and 7). This decrease in myocardial performance has been shown for septic shock in man (20,26), but was not reported previously in monkeys (2).

Another factor which may have contributed to the myocardial dysfunction is metabolic acidosis although there was adequate compensation with constant pH throughout the study. Hypoxia also can be eliminated since the PaO_2 of the endotoxin monkeys was greater than the PaO_2 of the control monkeys for the duration of the experiment. The mean hematocrit for the endotoxin monkeys was significantly higher after 6 hours than in the control monkeys, which have have influenced capillary perfusion but was likely to be less significant than the generalized circulatory impairment which resulted from pooling. Although MDF (19) or some other circulating depressant factor or abnormal metabolite released during shock could also influence myocardial function in the endotoxin group, this has been shown to be of no significance in the early or intermediate stages of shock (10).

From observations made after the recovery stage, it appears that fluid loading with colloid improves cardiac output in endotoxic shock to levels above control in the subhuman primate while the minute work improves to a level just slightly lower than normal. This benefit, however, can be costly in terms of pulmonary function if the rate of infusion produces transient overloading of the left ventricle.

SYNOPSIS-ABSTRACT

Myocardial performance was evaluated in rhesus monkeys after endotoxin shock, and the responses to fluid loading with colloid measured in both anesthetized control and experimental groups. Minute work and cardiac output (CO) were decreased in 5 monkeys after 6 hours endotoxin to levels significantly below control values. Infusing colloid to a mean LVEDP of 12-15 mm Hg increased both CO and minute work significantly but they remained one-half that of the control group of 4 primates after fluid loading. Improved cardiac performance persisted after infusion through a 30-minute recovery stage when LVEDP returned to normal. Simultaneous PAW pressures showed some correlation with LVEDP reading up to 6 mm Hg, but above that level the PAW underestimated the LVEDP by 3-6 mm Hg. Microscopic study showed that fluid loading produced comparable pulmonary edema in both groups, but endotoxin produced ultrastructural capillary lesions. A normal PAW pressure after fluid administration can occur after transient overloading of the left ventricle. Since interstitial pulmonary edema is not readily reversible, persistent respiratory insufficiency may result and the cause be unsuspected unless ventricular filling pressures are monitored during fluid administration.

REFERENCES

1. Bouchard, R. J., Gault, J. H., and Ross, J., Jr. Evaluation of pulmonary arterial end-diastolic pressure as an estimate of left-ventricular end diastolic pressure in patients with normal and abnormal left-ventricular performance. Circulation 44: 1072-1079, 1971.
2. Brockman, S. K., Thomas, C. S., Jr., and Vasko, J. S. The effect of Escherichia coli endotoxin on the circulation. Surg. Gynec. Obstet. 125: 763-774, 1969.
3. Burton, A. C. Peripheral circulation. Ann. Rev. Physiol. 15: 213, 1953.
4. Cavanagh, D., Rao, P. S., Sutton, D. M. C., dev Bhagat, B., and Bachmann, F. Pathophysiology of endotoxin shock in the primate. Am. J. Obstet. Gynec. 108: 705-722, 1970.
5. Coalson, J. J., Hinshaw, L. B., and Guenter, C. A. The pulmonary ultrastructure in septic shock. Exptl. Mol. Path. 12: 84-103, 1970.
6. Connolly, D. C., Kirklin, J. W., and Wood, E. H. The relationship between pulmonary artery wedge pressure and left atrial pressure in man. Circ. Res. 2: 434-440, 1954.
7. Gilbert, R. P. Mechanisms of the hemodynamic effects of endotoxin. Physiol. Rev. 40: 245-279, 1960.
8. Gilbert, R. P. Endotoxin shock in the primate. Proc. Soc. Exptl. Biol. Med. 111: 328-331, 1962.
9. Greenfield, L. J., Duncan, R. C., Parker, D. E. Response surface analysis of pulmonary surfactant hysteresis loops. J. Surg. Res. 9: 671-678, 1969.
10. Greenfield, L. J., McCurdy, J. R., Hinshaw, L. B., Elkins, R. C. Preservation of myocardial function during cross-circulation in terminal endotoxin shock. Surgery 72: 111-118, 1972.

11. Greenfield, L. J., Reif, M. E., Coalson, J. J., McCurdy, J. R., Elkins, R. C. Comparative effects of interstitial pulmonary edema produced by venous hypertension or hemodilution in perfused lungs. Surgery 71: 857-864, 1972.

12. Guenter, C. A., McCaffree, D. R., Davis, L. J., and Smith, V. S. Hemodynamic characteristics and blood gas exchange in the baboon. J. Appl. Physiol. 25: 504-510, 1968.

13. Guenter, C. A., Fiorica, V., and Hinshaw, L. B. Cardiorespiratory and metabolic responses to live E. coli and endotoxin in the monkey. J. Appl. Physiol. 26: 780-786, 1969.

14. Harrison, L. H., Beller, J. J., Hinshaw, L. B., Coalson, J. J., and Greenfield, L. J. Effects of endotoxin on pulmonary capillary permeability, ultrastructure and surfactant. Surg. Gynec. Obstet. 129: 723-733, 1969.

15. Hinshaw, L. B., Emerson, T. E., Jr., and Reins, D. A. Cardiovascular responses of the primate in endotoxin shock. Am. J. Physiol. 210: 335-340, 1966.

16. Hinshaw, L. B., Solomon, L. A., Reins, D. A., and Fiorica, V. Sympathoadrenal system and renal response to endotoxin in the primate. Nephron 4: 394-404, 1967.

17. Hinshaw, L. B., Shanbour, L., Greenfield, L. J., and Coalson, J. J. Mechanism of decreased venous return. Arch. Surg. 100: 600-606, 1970.

18. Kusajima, K., Webb, W. R., Wax, S. D., Parker, F. B., Jr., and Ozdemir, I. A. Hemodynamic effects of methylprednisolone on pulmonary microcirculation in hypovolemia. Physiologist 16: 369, 1973.

19. Lefer, A. M., and Glenn, T. M. Role of the pancreas in the pathogenesis of circulatory shock. In: The Fundamental Mechanisms of Shock, New York: Plenum Press, 1972, p. 326-330.

20. Lovett, W. L., Wangensteen, S. L., Glenn, T. M., and Lefer, A. M. Presence of a myocardial depressant factor in patients in circulatory shock. Surgery 70: 223-231, 1971.

21. MacLean, L. D., Mulligan, W. G., McLean, A. P. H., and Duff, J. H. Patterns of septic shock in man: a detailed study of 56 patients. Ann. Surg. 166: 543-562, 1967.

22. McKay, D. G., Margaretten, W., and Csavossy, I. An electron microscope study of endotoxin shock in rhesus monkeys. Surg. Gynec. Obstet. 125: 825-832, 1967.

23. Nies, A. S., Forsyth, R. P., Williams, H. E., and Melmon, K. L. Contribution of kinins to endotoxin shock in unanesthetized monkeys. Circ. Res. 22: 155-164, 1968.

24. Ross, J., Jr., Sonnenblick, E. H., Kaiser, J. A., Frommer, P. L., and Braunwald, E. Electroaugmentation of ventricular performance and oxygen consumption by repetitive application of paired electrical stimuli. Circ. Res. 16: 332-341, 1965.

25. Scheinman, M., Evanes, C. T., Weiss, A., and Rapeport, E. Relationship between pulmonary artery end-diastolic pressure and left ventricular filling pressure in patients in shock. Circulation 47: 317-323, 1973.

26. Siegel, J. H., Greenspan, M., and Del Guercio, L. R. M. Abnormal vascular tone, defective oxygen transport and myocardial failure in human septic shock. Ann. Surg. 165: 504-517, 1967.

27. Weil, M. H., MacLean, L. D., Visscher, M. B., and Spink, W. W. Studies on the circulatory changes in the dog produced by endotoxin from gram-negative microorganisms. J. Clin. Invest. 35: 1191-1198, 1956.

28. Wiggers, C. J. Pulmonary wedged catheter pressures (Editorial). Circ. Res. 1: 371, 1953.

29. Wyler, F., Forsyth, R. P., Nies, A. S., Neutze, J. H., and Melmon, K. L. Endotoxin-induced regional circulatory changes in the unanesthetized monkey. Circ. Res. 24: 777-786, 1969.

FIGURE LEGENDS

Figure 1. Changes in mean hematocrit (Hct) in endotoxin-shocked (solid line) and control (dashed line) primates after 6 hours and following colloid infusion. The recovery measurement was made 30 minutes after cessation of infusion. Statistically significant differences (*, $p<0.05$) were observed in the endotoxin group at 6 hours and after loading when compared to control.

Figure 2. Changes in mean arterial pH in endotoxin-shocked (solid line) and control (dashed line) primates after 6 hours and following fluid loading by colloid. Statistically significant (*, $p<0.05$) differences between groups were observed after loading and following a 30 minute recovery period.

Figure 3. Alterations in respiratory rate and arterial blood gases (PaO_2 and $PaCO_2$) in endotoxin-shocked (solid line) and control (dashed line) primates after 6 hours and following colloid fluid loading and recovery. The endotoxin group showed higher respiratory rates and PaO_2 with lower $PaCO_2$ although the differences were not statistically significant.

Figure 4. Alterations in mean systemic arterial pressure expressed as percent control measured after 6 hours in endotoxin-shocked (solid line) and control (dashed line) primates. The response to fluid infusion with colloid to an LVEDP of 15 mm Hg is shown for each animal (#3-11) during infusion and after a recovery period of 30 minutes.

Figure 5. Correlation of PAW and LVEDP pressures shows a tendency for PAW to exceed slightly the measured LVEDP up to pressure of 6 mm Hg beyond which the PAW tends to underestimate the LVEDP.

Figure 6. Alterations in cardiac output (CO) and LVEDP shown for endotoxin-shocked (solid line) and control (dashed line) primates after 6 hours and following colloid infusion and a 30-minute recovery period. As shown at the top, the response to left ventricular loading is less in the endotoxin-groups than in controls but continues to improve during the recovery period. The pressure work performed shown in the center graph shows a greater discrepancy between the groups with less recovery after loading, and comparable depression of minute work and response to loading is observed below.

Figure 7. Endotoxin-lung specimen. Low power micrograph depicting moderate alveolar wall collapse with focal pulmonary edema. The walls appear to be hypercellular. Hematoxylin and eosin, 63 X.

Figure 8. Control-lung specimen. Low power electron micrograph in which the capillary (C) contains cellular remnants intermingled with the Pelikan ink (arrow). There is minimal edema noted within the perivascular space (P). The alveolar spaces (A) are free from transudate. Lead citrate and uranyl acetate, 7300 X.

Figure 9. Endotoxin-lung specimen. The capillary is filled with polys (N), one of which has lost its cytoplasmic membrane integrity. The plasma transudate contains free specific granules and cellular debris associated with the Pelikan ink. The endothelium shows focal cytoplasmic disruption (double arrow). There is minimal perivascular space (P) edema. The alveolar spaces (A) are free from transudate. Lead citrate and uranyl acetate, 7300 X.

Figure 10. Control-heart specimen. Low power electron micrograph shows the presence of several myocardial fibers (M) and capillaries (C). Note that the endothelium of the capillary is thin with distinct

intercellular junctions. There are multiple Pelikan ink particles present. The interfiber space (I) is normal in contents and width. Lead citrate and uranyl acetate, 4540 X.

Figure 11. Endotoxin-heart specimen. The muscle fibers (M) noted in cross-section show the presence of interfiber edema with separation of the myofibrils and mitochondria. Within the interfiber spaces (I), there is an edematous transudate. The capillary (C) within this connective tissue compartment shows severe edema (E) in two of the three endothelial cytoplasmic portions. Several Pelikan ink particles are noted within the capillary lumen. Lead citrate and uranyl acetate, 5900 X.

Figure 12. Endotoxin-heart specimen. The endothelial cytoplasm of the myocardial capillary (C) shows edema with focal bleb-like formations (arrow). Several blebs (B) are free in the plasma. The interfiber space (I) contains increased amounts of fluid. Lead citrate and uranyl acetate, 8000 X.

Figure 13. Schematic representation of the possible effect of volume loading with fluid to a point of transient ventricular overloading. The resulting development of interstitial pulmonary edema would tend to be self-perpetuating while the hemodynamics returned to normal.

TABLE 1

ALTERATIONS IN HEART RATE (HR) IN CONTROL AND ENDOTOXIN-SHOCK PRIMATES FOLLOWING COLLOID INFUSION AND RECOVERY FOR 30 MINUTES

	SALINE CONTROL							ENDOTOXIN							
	#3	#4	#5	#9	$\bar{M}$	S.D.	S.E.	#3	#7	#8	#10	#11	$\bar{M}$	S.D.	S.E.
Control	170	155	107	185	154.2	33.8	17	175	185	170	190	180	180	7.906	3.536
+6 hr	210	170	200	220	200	21.6	10.8	230	245	235	240	220	234	9.618	4.301
5cc Pl/kg	200	165	220	210	199	24	12	220	225	230	230	215	224	6.519	2.915
10 cc Pl/kg	200	165	210	205	195	20.4	10.2	210	225	220	220	215	218	5.701	2.549
15cc Pl/kg	190	160	210	205	191	22.5	11.2	205	210	215	220	220	214	6.519	2.915
20cc Pl/kg			200	205	202.5	3.5	2.5	200	210	210	215	215	210	6.124	2.739
25cc Pl/kg			200		200			200	210	205	210	218	208	5.701	2.549
30cc Pl/kg			200		200				205	205	210	200	205	4.082	2.041
35cc Pl/kg			195		195				200	195			197.5	3.536	2.500
40cc Pl/kg										190			190		
Recovery		165		230	197.5	46	32.5		195	190	210	200	198.7	8.539	

TABLE 2

ALTERATIONS IN MEAN SYSTEMIC ARTERIAL PRESSURE (MSAP) IN CONTROL AND ENDOTOXIN-SHOCK PRIMATES FOLLOWING COLLOID INFUSION AND RECOVERY FOR 30 MINUTES

	SALINE CONTROL							ENDOTOXIN							
	#3	#4	#5	#9	$\bar{M}$	S.D.	S.E.	#6	#7	#8	#10	#11	$\bar{M}$	S.D.	S.E.
Control	135	130	145	135	136.2	6.3	3.1	165	150	120	205	145	157	31.3	14.0
+6 hr	115	140	130	135	130	10.8	5.4	135	70	90	145	120	112	31.3	14.0
5cc Pl/kg	155	145	140	150	147.5	6.4	3.2	115	80	100	150	120	113	25.9	11.6
10cc Pl/kg	135	140	150	145	142.5	6.4	3.2	135	85	90	150	120	116	26.1	12.6
15cc Pl/kg	145	150	145	145	146.2	2.5	1.2	130	80	70	160	115	111	36.8	16.5
20cc Pl/kg			150	145	147.5	3.5	2.5	120	75	75	150	110	106	31.9	14.3
25cc Pl/kg			140		140			110	75	65	150	105	101	33.4	14.9
30cc Pl/kg			140		140				70	65	145	95	93.7	36.6	18.3
35cc Pl/kg			130		130				70	60			65	7.1	5.0
40cc Pl/kg										55			55		
Recovery		160		115	137.5	31.8	22.5		80	70	145	90	96.2	33.5	16.8

TABLE 3

ALTERATIONS IN LEFT VENTRICULAR END-DIASTOLIC PRESSURE (LVEDP) IN CONTROL AND ENDOTOXIN-SHOCK PRIMATES FOLLOWING COLLOID INFUSION AND RECOVERY FOR 30 MINUTES

	SALINE CONTROL						ENDOTOXIN						
	#3	#4	#5	#9	$\bar{M}$	S.E.	#6	#7	#8	#10	#11	$\bar{M}$	S.E.
Control	2.5	2	1	1	2.1	0.43	3	1	3	6	0	2.6	1.03
+6 hr	1	1.5	1	1	1.1	0.12	3	1	0.5	1	1	1.3	.44
5cc Pl/kg	1	2	1	1	1.2	0.25	5	0.5	2	0	1	1.7	.89
10cc Pl/kg	7	4	1		4	1.73	5	2	2	1	3	2.6	.68
15cc Pl/kg	17	8	2	5	8	3.2	8	3	2.5	6	3	4.5	1.1
20cc Pl/kg		12	1	15	8	7	10	6	3.5	9	6	6.9	1.2
25cc Pl/kg			4		4		12	9	6.5	11	10	9.7	.94
30cc Pl/kg			14		14			11	9	14	12	11.5	1.04
35cc Pl/kg			15		15			14	11			12.5	1.50
40cc Pl/kg									12			12	
Recovery		4		2	3	1		3	7	5	2	4.2	1.11

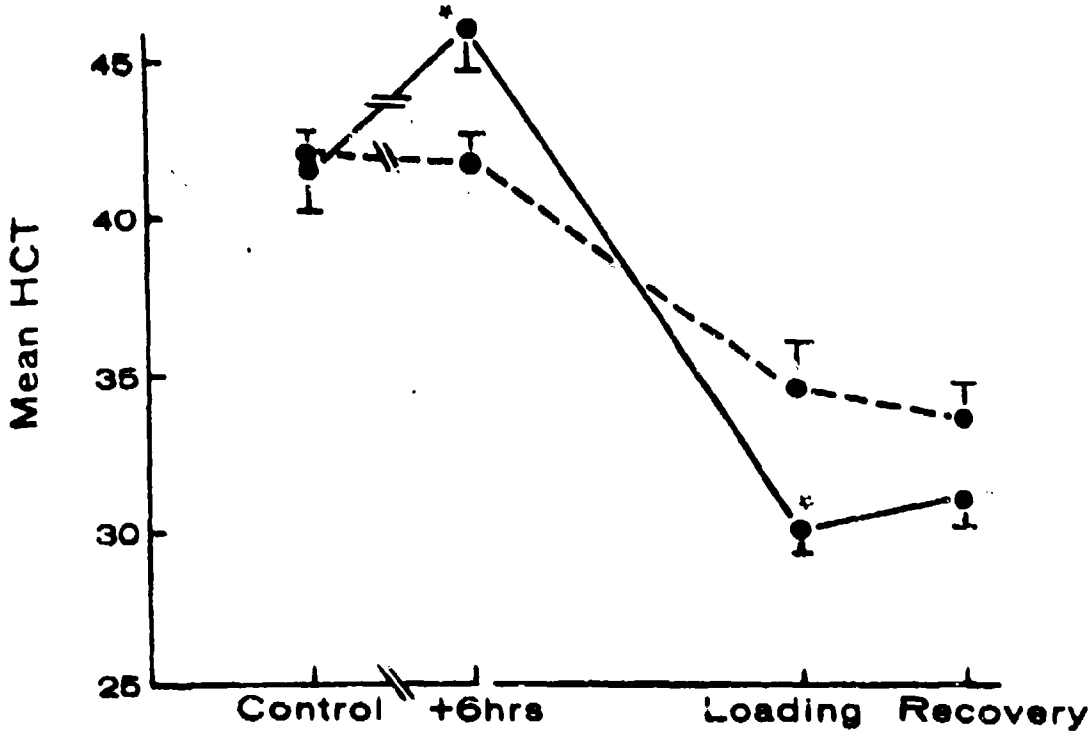

FIGURE 1

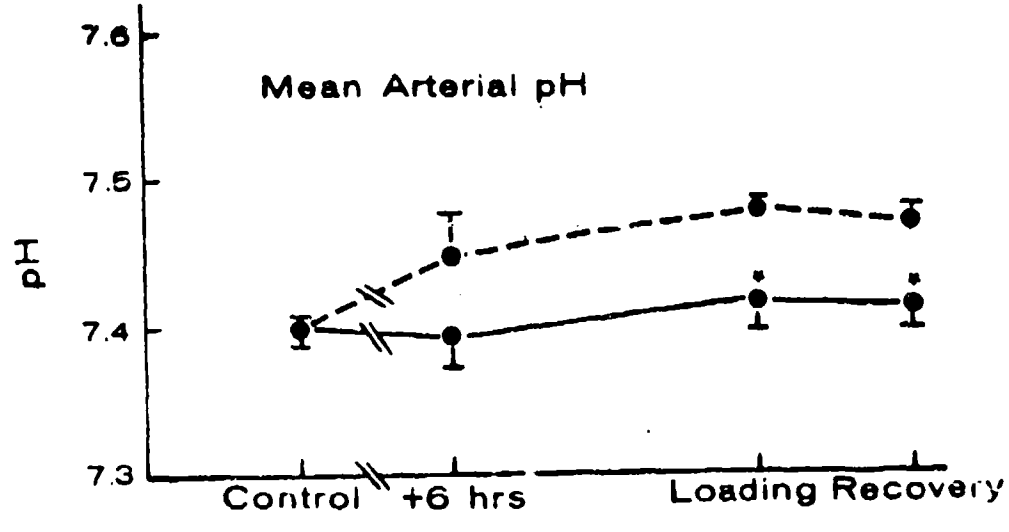

FIGURE 2

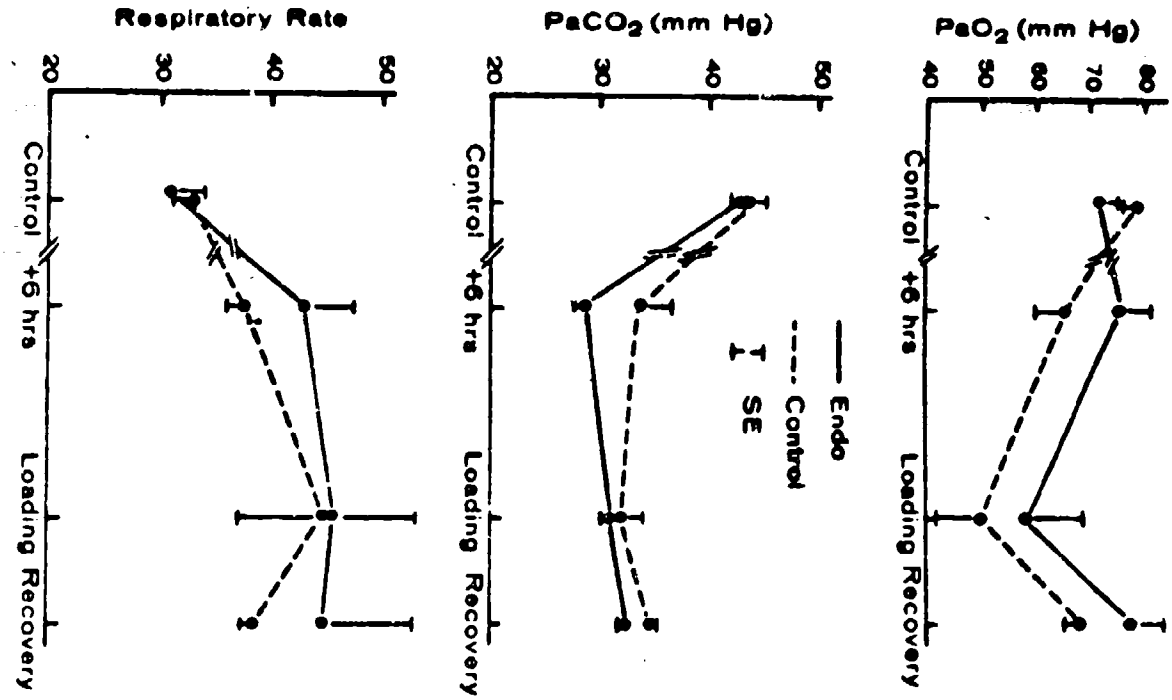

FIGURE 3

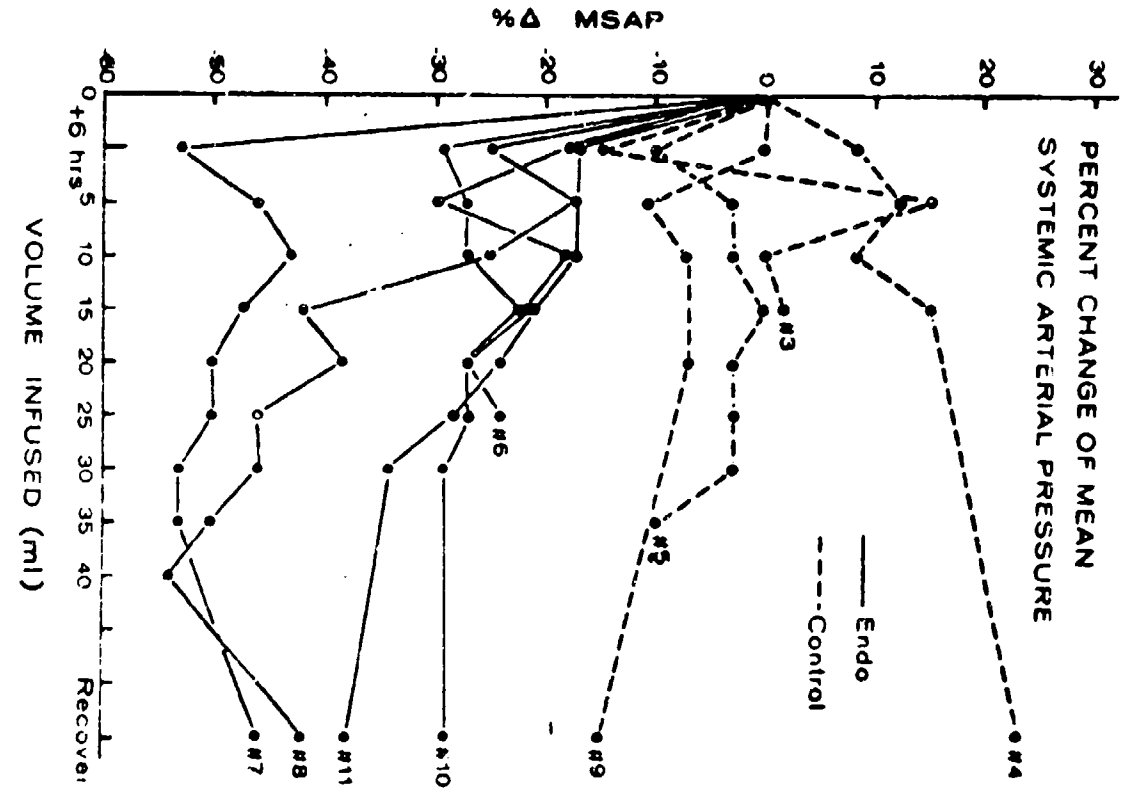

FIGURE 4

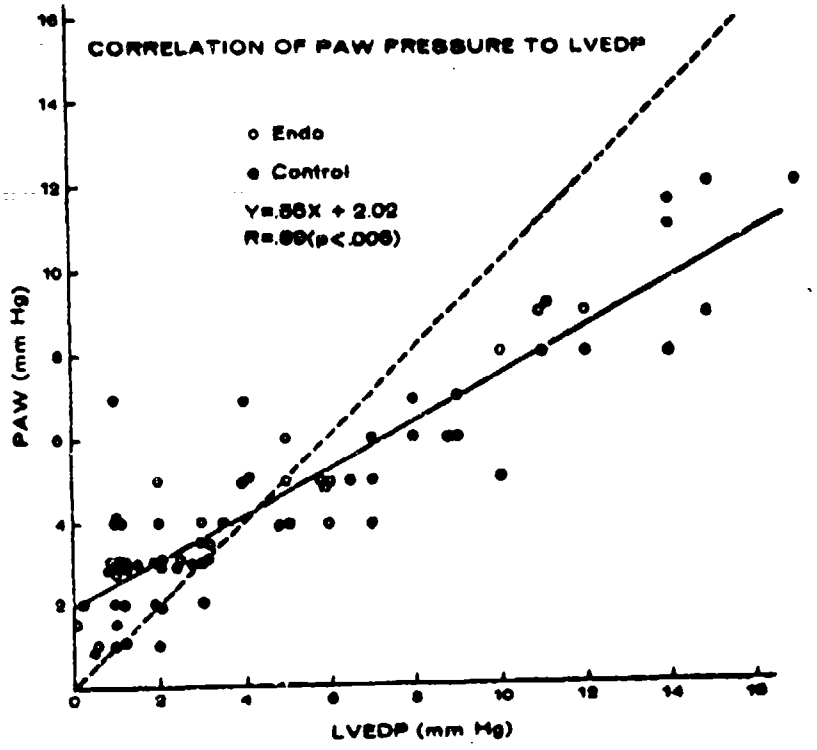

FIGURE 5

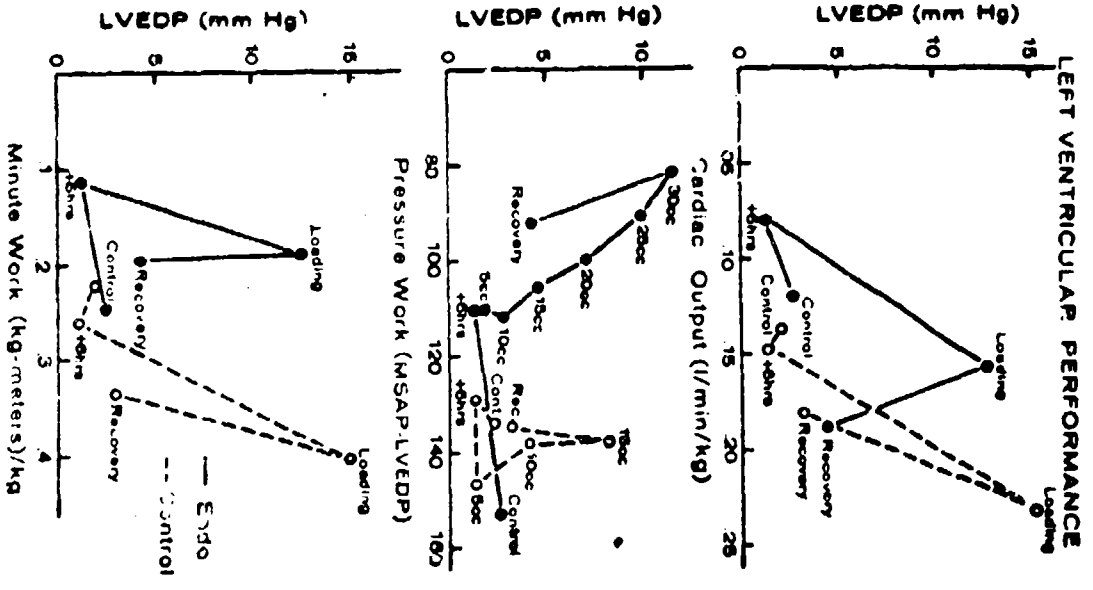

FIGURE 6

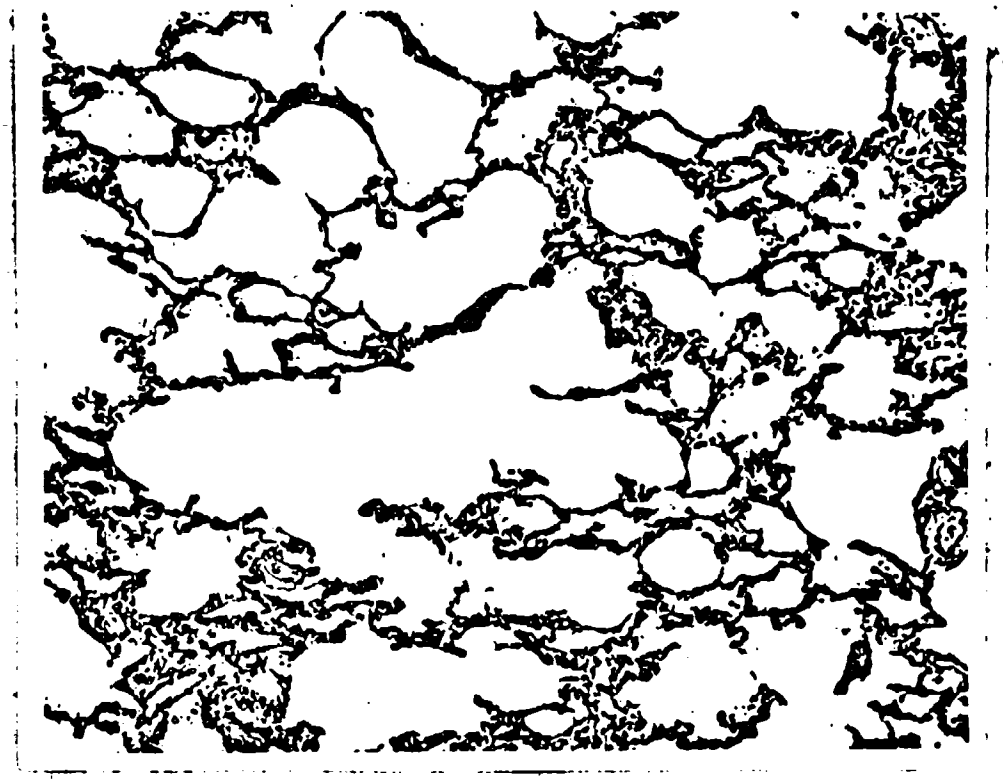

FIGURE 7

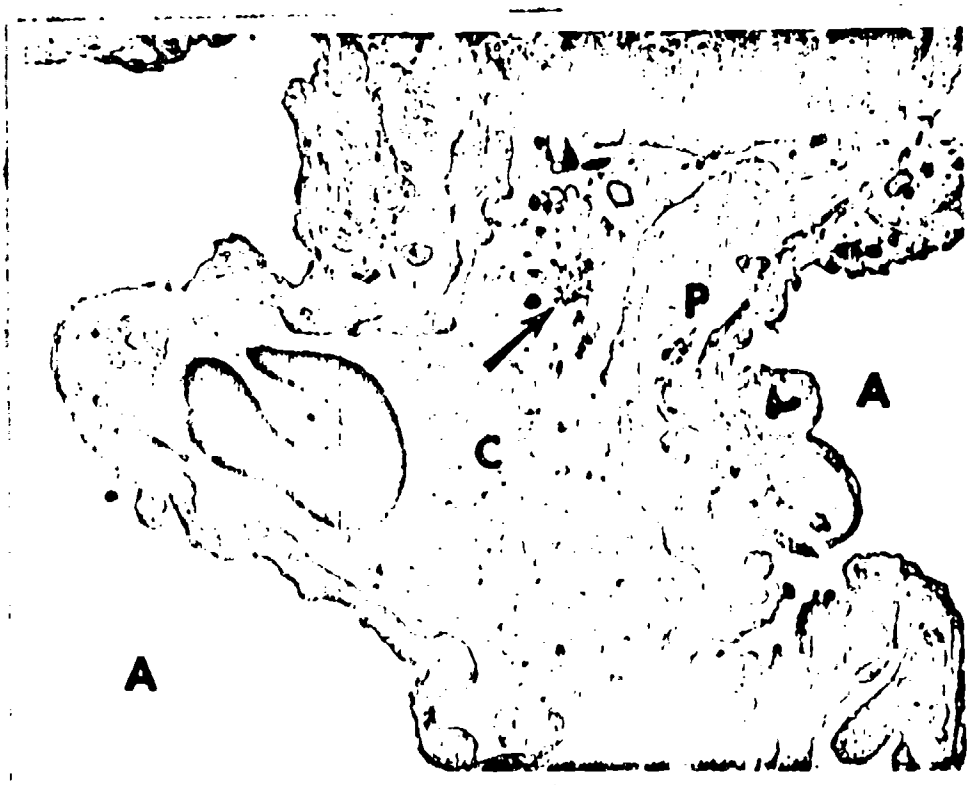

FIGURE 8

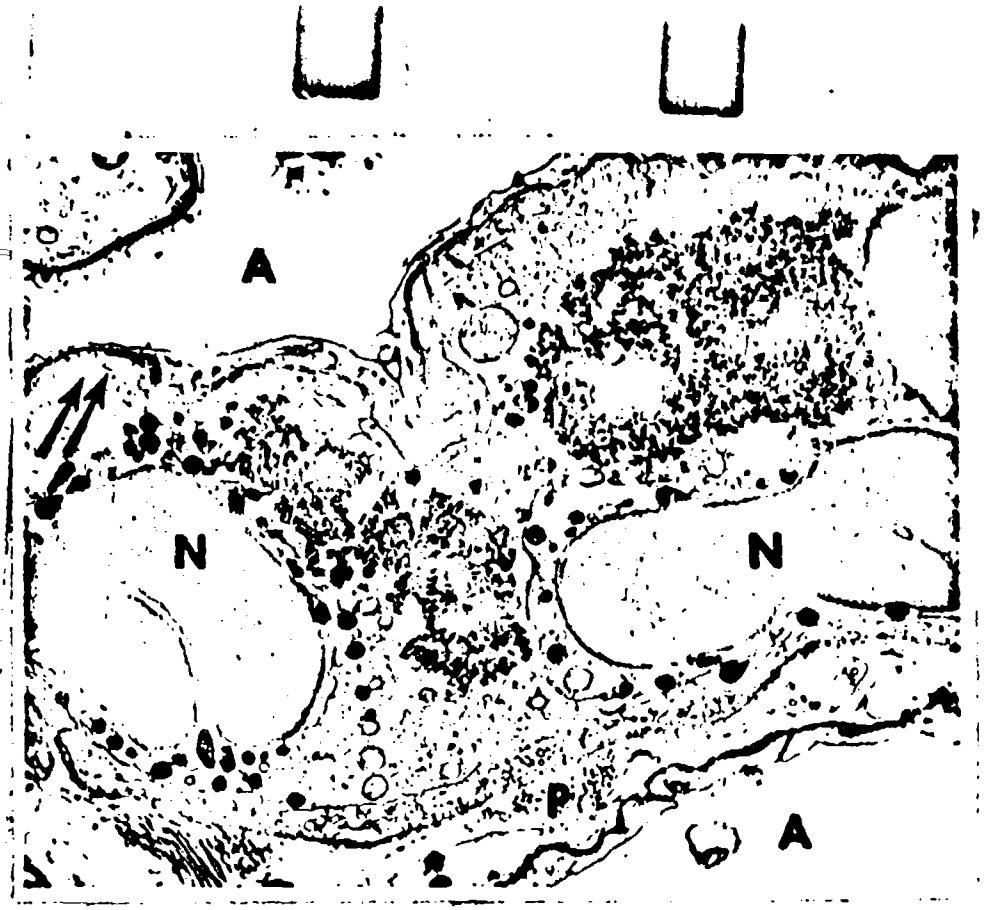

FIGURE 9

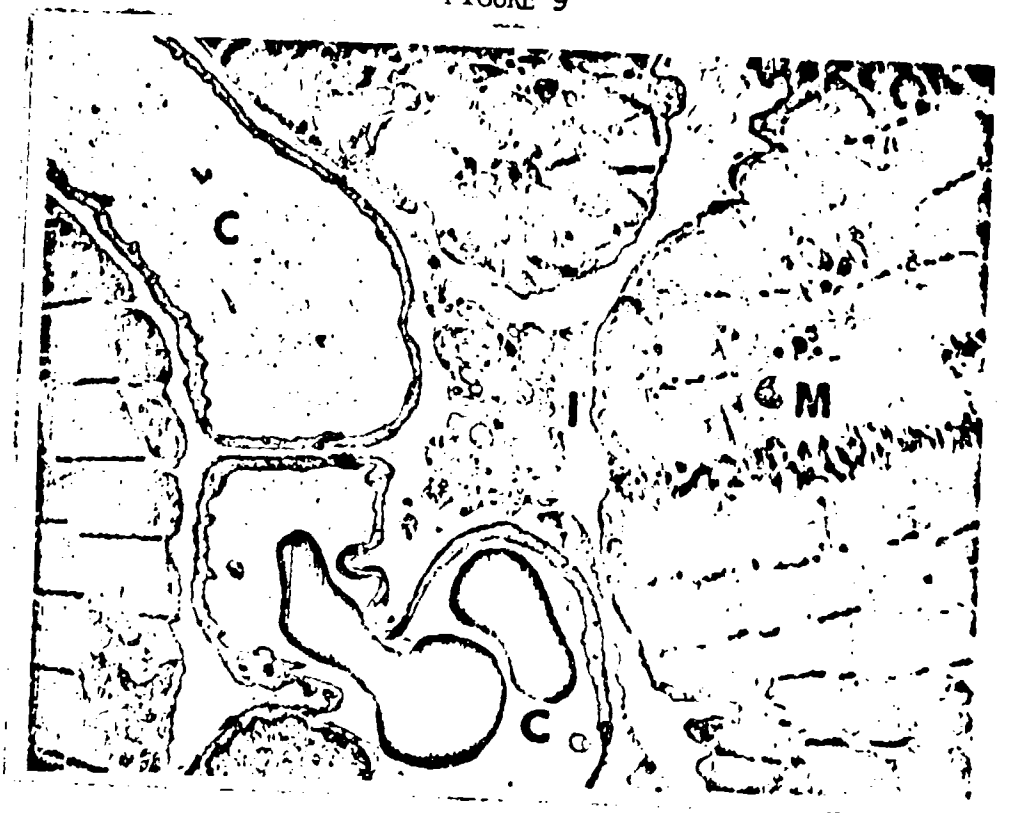

FIGURE 10

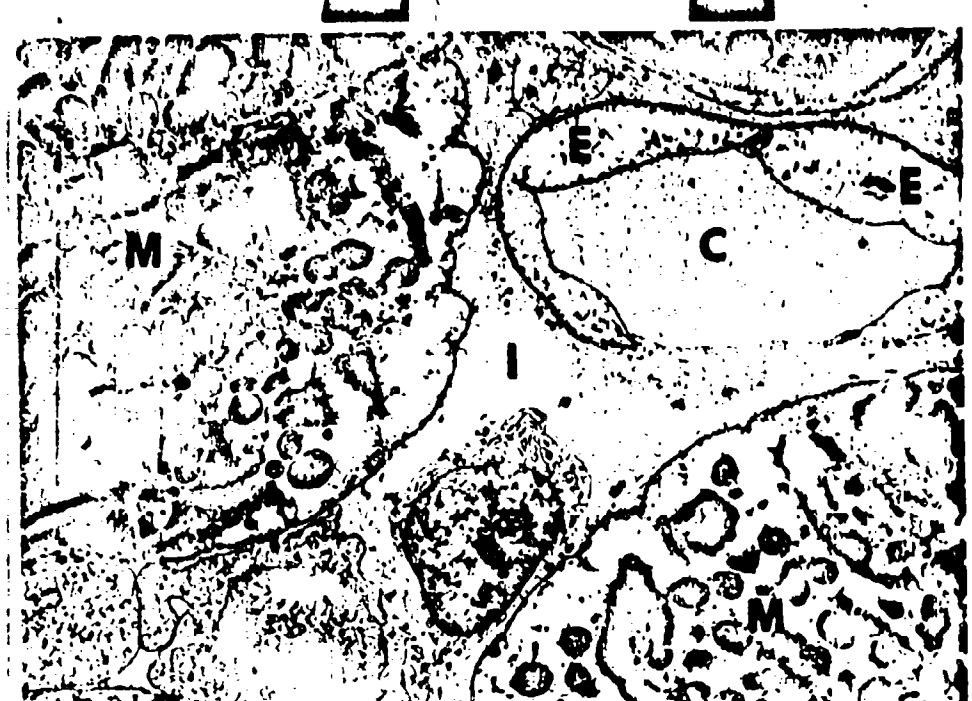

FIGURE 11

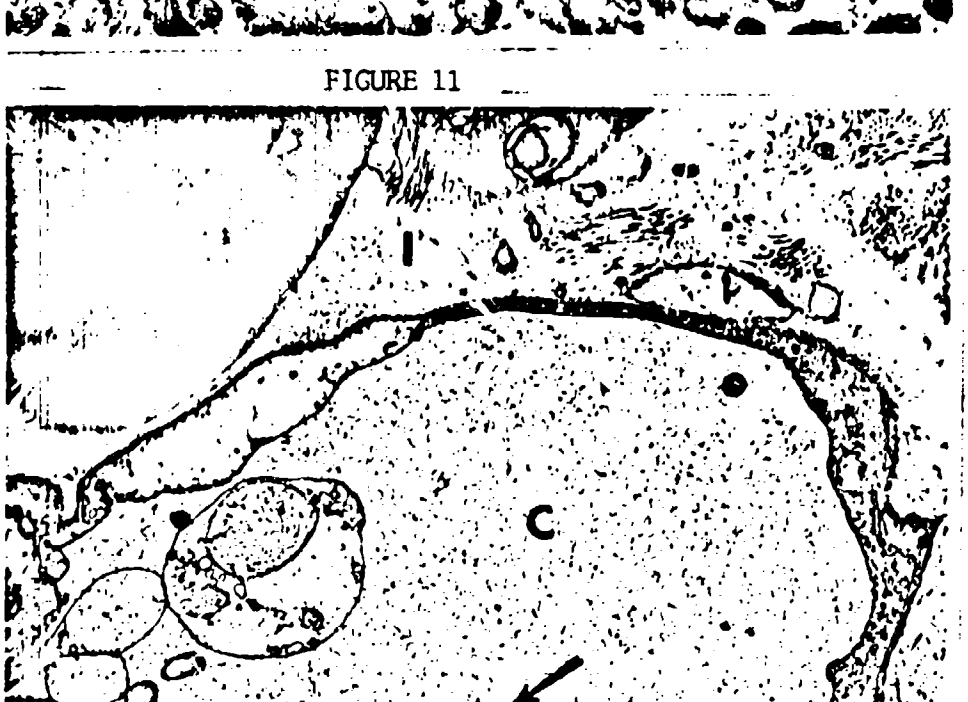

FIGURE 12

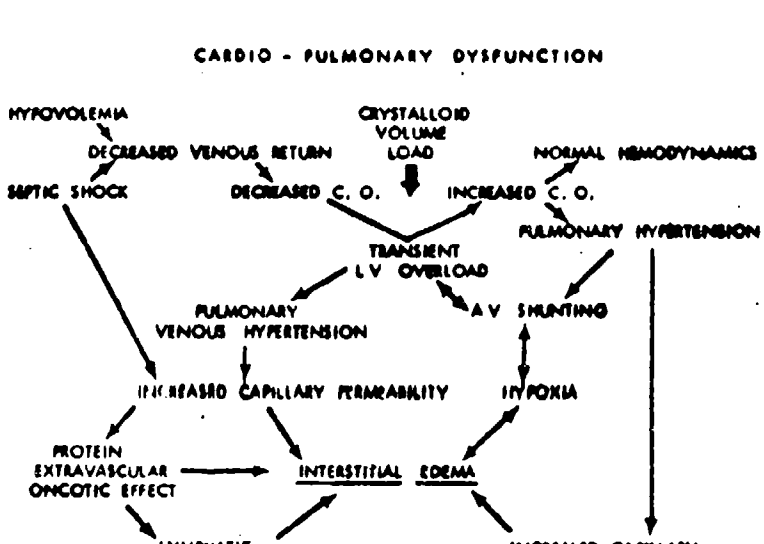
CARDIO - PULMONARY DYSFUNCTION
HYPOVOLEMIA
CRYSTALLOID VOLUME LOAD
DECREASED VENOUS RETURN
NORMAL HEMODYNAMICS
SEPTIC SHOCK
DECREASED C. O.
INCREASED C. O.
PULMONARY HYPERTENSION
TRANSIENT LV OVERLOAD
PULMONARY VENOUS HYPERTENSION
A V SHUNTING
INCREASED CAPILLARY PERMEABILITY
HYPOXIA
PROTEIN EXTRAVASCULAR ONCOTIC EFFECT
INTERSTITIAL EDEMA
LYMPHATIC OVERLOADING
INCREASED CAPILLARY HYDROSTATIC PRESSURE

FIGURE 13